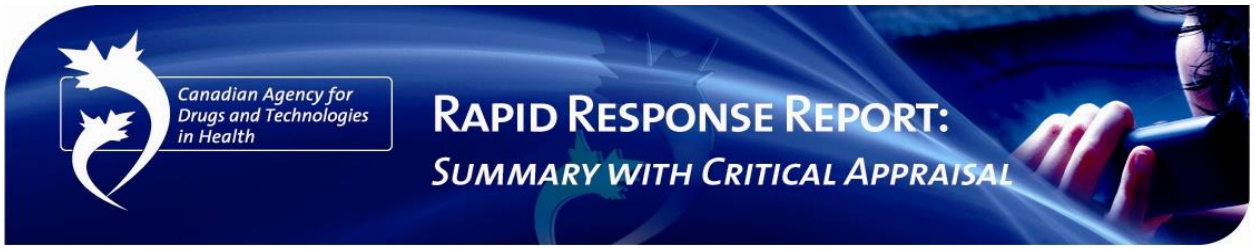

TITLE: C1 Esterase Inhibitor for Prophylaxis against Hereditary Angioedema Attacks: A Review of the Clinical Effectiveness, Cost-Effectiveness, and Guidelines

DATE: 24 April 2015

CONTEXT AND POLICY ISSUES

Hereditary angioedema (HAE) is an autosomal dominant disease, characterized by episodes of painful excess fluid build-up, typically affecting the bowels, face and upper airway, body trunk, genitalia, and extremities.[1] HAE is caused by a deficiency in C1 esterase inhibitor (C1-INH), and is estimated to affect 1 in 50,000 individuals, with no differences in prevalence based on gender or race.[1] Typically, HAE presents within the first or second decade of life, and persists throughout, a patient's lifetime.[2] There are three forms of HAE: the most common form being characterized by a deficiency in functional C1-INH (type I) and thought to account for approximately 85% of cases; the second most common form, thought to affect 15% of cases, is characterized by a functionally impaired C1-INH (type II); the third, and most rare form, is characterized by normal C1-INH antigenic and functional levels, and likely caused by an unknown genetic mutation.[2] HAE attacks in the face and upper airway can cause obstruction and be potentially life threatening.[2] Patients may experience certain triggers for HAE attacks, including physical or emotional stress, infection, fluctuations in hormones, and pregnancy.[2]

HAE is associated with significant mortality and morbidity, requiring effective options for treatment and management. Management of HAE may include treatment for acute attacks, or short- or long-term prophylaxis for prevention of HAE attacks. Need for tailored treatment may depend on a patient's age, clinical disease history, including severity of attacks, attack frequency, attack site (e.g., face and upper airway), and exposure to known HAE attack triggers (e.g., invasive procedures).[2] Short-term prophylaxis may be required before a medical procedure, which can be a trigger for an attack.[2] Long-term prophylaxis may be appropriate for patients who experience a high frequency of attacks, or have poor control over acute attacks.

Treatment and prevention options may include: attenuated androgens, which may have severe side effects; antifibrinolytics, which have uncertain efficacy; bradykinin antagonist (icatibant); recombinant kallikrein inhibitor (ecallantide); or C1-INH replacement.[2] Previous CADTH work has been done on C1-INH for the treatment of HAE attacks.[3] However, C1-INH replacements, for prophylactic use, are the intervention of interest for this review. Currently, two C1-INH

replacements are approved for use in Canada (Berinert for acute treatment, and Cinryze for long-term prophylaxis).[4] Administration of these C1-INH have been associated with thromboembolic events, which are a particular adverse event of interest.[2]

The purpose of this review is to assess evidence on the clinical effectiveness, cost-effectiveness, and evidence-based guidelines regarding the prophylactic use of C1-INH against HAE attacks.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of C1 esterase inhibitor as prophylaxis against hereditary angioedema attacks?

2. What is the cost-effectiveness of C1 esterase inhibitor as prophylaxis against hereditary angioedema attacks?

3. What are the evidence-based guidelines for the prophylactic use of C1 esterase inhibitor in hereditary angioedema?

KEY FINDINGS

One systematic review, one RCT, nine non-randomized studies, and one evidence-based guideline were identified regarding the prophylactic use of C1 Esterase Inhibitor (C1-INH) for hereditary angioedema attacks. No cost-effectiveness studies were identified. All studies, including the evidence-based guidelines, found C1-INH to be effective, and relatively safe, in the prevention of hereditary angioedema attacks when used as either short-term prophylaxis or long-term prophylaxis. However, these studies are marked by several limitations, and the findings should be interpreted with caution.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD), and ECRI databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and March 24, 2015.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria	
Population	Patients with hereditary angioedema (HAE)
Intervention	Prophylactic C1 esterase inhibitor (i.e., Berinert, Cinryze)
Comparator	Active comparators (e.g., on-demand C1 esterase inhibitor, Firazyr [icatibant], Kalbitor [ecallantide], Ruconest [C1 esterase inhibitor – recombinant], attenuated androgens [e.g., danazol, oxandrolone], tranexamic acid) Placebo No treatment No comparator
Outcomes	Q1: Clinical effectiveness (e.g., symptom reduction/management, time to symptom relief) Safety (e.g., anaphylaxis, headache, GI symptoms, thromboembolic events, increased pain associated with HAE attacks) Q2: Cost-effectiveness Q3: Guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2010.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using Assessment of Multiple Systematic Reviews (AMSTAR) tool,[5] randomized and non-randomized studies were critically appraised using the Downs and Black checklist,[6] and guidelines were assessed with the AGREE II instrument.[7] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 434 citations were identified in the literature search. Following screening of titles and abstracts, 408 citations were excluded and 26 potentially relevant reports from the electronic search were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 18 publications were excluded for various reasons, while 12 publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

The following provides a summary of the characteristics. Details of the study characteristics of individual studies are located in Appendix 2.

Study Design

A total of 12 publications reporting on eight studies were identified regarding the clinical effectiveness of prophylactic use of C1 esterase inhibitor (C1-INH) for hereditary angioedema (HAE). These publications included: one systematic review,[8] one crossover randomized controlled trial (RCT),[9] and nine non-randomized studies.[10-18]

The systematic review[8] included eight studies regarding long-term prophylaxis therapy (two prospective cohort studies, one retrospective survey study, and five case reports). Also included were 34 studies regarding short-term prophylactic use (21 case reports, six case-series studies, two cohort studies, four retrospective survey studies, and one prospective and retrospective survey study).[8] No language or date restrictions were imposed during the literature search.[8]

The RCT[9] consisted of two consecutive 12 week periods. Patients were randomized to receive the study drug or placebo (saline) for a period of 12 weeks, then crossed over to the other study arm for an additional 12 week period.[9] C1-INH (1000 units) was administered every three to four days, though patients were able to receive open-label C1-INH as rescue therapy for any break through attacks.

Two of the non-randomized studies[15,17] were post-hoc analyses of data from the RCT[9] and its open-label extension study.[18] One non-randomized study[14] was a retrospective analysis of a previous open-label extension study.[18] Study designs for the non-randomized studies also included a phase four open-label trial,[13] patient and physician survey,[11] analysis of an open patient registry,[10] a retrospective chart review,[12] and prospective cohort study.[16]

Additionally, one evidence-based guideline[4] was identified regarding the prophylactic use of C1-INH for HAE.

Country of Origin

The systematic review[8] originated from Germany, the RCT[9] from the United States (USA), and the evidence-based guidelines[4] were developed in Canada. Seven of the non-randomized studies[10,11,13-15,17,18] were from the USA, one[13] was from Canada, and one[16] was from Hungary.

Patient Population

The systematic review[8] did not restrict the age of interest or patient population, other than patients having HAE. The RCT[9] had an inclusion criteria that patients had to be over 6 years of age; the mean age, and standard deviation, of patients that started on placebo and crossed over to C1-INH was 34.5 ± 14.8 years, while the mean age, and standard deviation, of patients that started on C1-INH and crossed over to placebo was 41.7 ± 19.3 years.

Six of the non-randomized studies included adults and pediatric patients.[10,13,14,16-18] One non-randomized study did not specify the age of patients.[11] One non-randomized study included only adults.[12] Minimum and maximum ages of patients across all included studies were 2.2 years,[16] and 82 years,[18] respectively.

Two non-randomized studies specifically reported on prophylaxis in vulnerable patient populations; one regarding the use of C1-INH in pregnant patients,[14] and one regarding use in pediatric patients (ranging from 2 to 17 years).[15]

The guideline[4] did not specifically address pediatric or obstetric patients, but rather developed the guidelines for health care providers of patients with HAE types I, II and III.

Interventions and Comparators

The systematic review[8] specifically evaluated the efficacy and safety of the C1-INH concentrate Berinert (CSL Behring, Marburg, Germany). Short-term prophylaxis and long-term prophylaxis were both indications of interest.[8]

The RCT[9] study drug of interest was nanofiltered C1 inhibitor concentrate (C1-INH-nf) (Cinryze, ViroPharma), and compared its use to placebo (saline). Its indication for use was long-term prophylaxis, administered every 3 to 4 days for 12 weeks; open-label rescue therapy with C1-INH was permitted if patients experienced breakthrough acute attacks.[9] The studies by Baker et al.,[14] Lumry et al.,[15] and Grant et al.[17] were post-hoc analyses of this trial, regarding use in vulnerable subgroups,[14,15] and available data on patients using C1-INH for short-term prophylaxis.[17] The study by Zuraw and Kalfus[18] was an open-label extension of the identified RCT,[9] involving the same study drug and indication, but there was no comparator.

One[16] of the non-randomized studies compared plasma derived C1-INH (pdC1-INH) delivered one hour before a procedure to other drugs, danazol and tranexamic acid. The study by Bernstein et al.[13] used escalating doses of C1-INH-nf, in 1500 units, 2000 units and 2500 units for 12 week periods; there was no other drug comparator or placebo. The study by Gavigan et al.[12] reported on the use of C1-INH (Berinert) for short-term prophylaxis prior to invasive surgery. Nanda et al.[11] reported on the use of plasma-derived C1-INH (pdC1-INH) for short-term prophylaxis before undergoing a procedure. The study by Busse et al.[10] reported on the use of C1-INH (Berinert) for prophylaxis.

Outcomes

The systematic review[8] reported on clinical effectiveness and safety of C1-INH as outcomes of interest. Clinical effectiveness and safety were also outcomes of interest for the RCT,[9] and seven of the non-randomized studies.[11,13-18] Two non-randomized studies[10,12] only reported on safety. Recommendations in the guideline[4] were graded on the level of evidence, and the strength of the recommendation using an adaptation of the Grading of Recommendations Assessment, Development and Evaluation methodology. Level of evidence grading was based on the individual study, as well as the collective literature; recommendations were graded based on the quality of evidence, values and preferences, costs, and balance of desirable and undesirable affects.[4] More detailed outcomes are explored in the summary of findings below, and Appendix 4.

Summary of Critical Appraisal

The following provides a summary of the critical appraisal. Details of the critical appraisal of individual studies are located in Appendix 3.

The systematic review,[8] provided clearly stated objectives and key research questions, evidence for duplicate study selection and data extraction. Additionally, the search strategy was not limited by language or date restrictions, however, the search strings used were not stated and no medical subject headings terms were provided. Methodology for the summary of findings

was appropriate; a descriptive summary of the findings was performed, as meta-analysis was deemed unfeasible. There was no exploration into publication bias. The systematic review also limited the literature to studies reporting on C1-INH Berinert (CSL Behring, Marburg, Germany), and the summary findings may not be generalizable to other C1-INH products.

The included RCT[9] was marked by several limitations. Some of these limitations were inherent to the nature of the disease and, due to its rarity, few patients participated in the study; no power calculations were reported by the study authors.[9] Confounding factors may also play a factor in the RCT, as three out of 22 patients reported androgen therapy at baseline, but there was no exploration into any possible effect this might have in the study results. Study blinding and patient allocation were uncertain and not well reported. Additionally, patients were eligible for the long-term prophylaxis study if they had a higher frequency of attacks than the source HAE population, and findings from this study may not be generalizable outside of this patient population. However, the RCT did have well reported objectives and primary outcomes.

The other nine included clinical studies[10-18] were limited by the lack of randomization which may introduce selection bias. Many also did not have comparator data.[10-14,17,18] Comparator data would have added context regarding the place in therapy for prophylactic C1-INH, compared with either on-demand C1-INH or other therapeutic options, as well as providing more certainty that the outcomes could be attributed to C1-INH use. Another limitation, similar to the RCT, was the small number of patients available for study, with six studies reporting on 20 or fewer patients, but did not provide power calculations.[10-15] Only one study[13] specifically reported that it was not sufficiently powered to determine drug efficacy, but did not provided specific calculations. Other limitations include self-reported outcomes[11] which are subject to recall bias. The findings for the studies by Grant et al.,[17] Lumry et al.,[15] and Baker et al.[14] must be interpreted with caution as these were post-hoc analyses of the RCT[9] data. Findings from these studies should be considered exploratory. All nine non-randomized studies[10-18] had clearly stated objectives. Other strengths include, being a large survey of HAE patients,[11] a multinational study reflective of clinical practice,[10] including comparison data on other drugs,[16] and reporting on use in vulnerable patient populations which may be of particular interest in clinical practice.[14,15]

The guideline[4] was well done overall, with clearly stated recommendations which were graded based on level of evidence and the strength of the recommendation (consensus reached). The guideline also included clinical considerations to provide context surrounding the recommendations provided. However, costs and barriers to guideline implementation were not included, and special populations of interest (pediatric and obstetric patients) were not addressed. The methodological review was uncertain as it was not reported whether the search had multiple reviewers screening literature and extracting data.

Overall, the included studies had major limitations, including small patient populations and lack of comparator data. Findings from the included studies must be interpreted with caution.

Summary of Findings

The following provides a summary of the study findings. Details of the study findings are located in Appendix 4.

What is the clinical effectiveness of C1 esterase inhibitor as prophylaxis against hereditary angioedema attacks?

Systematic Review

The authors of the systematic review[8] provided a descriptive analysis of the findings as a meta-analysis was not possible. For short-term prophylaxis (STP), use of C1-INH was captured for 195 patients for 293 occasions. The majority of occasions (155 out of 293) were for dental procedures. One cohort study reported that no HAE complications were experienced during or after surgery for two patients administered C1-INH 30 minutes beforehand. Another cohort study regarding 171 patients for 705 tooth extractions, had a rate of facial swelling or laryngeal edema of 21.5% of 577 extractions when prophylaxis was not used, compared to 12.5% of 138 extractions where prophylaxis was used. Five survey studies (64 cases) reported no cases of HAE when C1-INH was used as prophylaxis. One case study reported on the use of C1-INH 1 hour before surgery for 71 procedures in 51 patients, with no cases of angioedema. No cases of HAE occurred in an additional five case series (10 cases), and 21 case reports when C1-INH was used as prophylaxis.

For long-term prophylaxis use, a reduction in symptom intensity was reported by one prospective cohort study, where 14 patients received C1-INH as LTP for an average of nine years (93.3% of attacks were considered severe without the use of prophylaxis, compared to 3.8% with prophylaxis). A decrease in attack frequency was reported by another prospective cohort study, where 15 out of 30 patients who before treatment had previously experienced one or two attacks per week did not report any HAE attacks while on LTP (C1-INH two to three times per week). A retrospective study reported no episodes of HAE for two pregnant patients (500 U of pdC1-INH administered intravenously, once per week). An additional five cases studies reported adequately controlled HAE with the use of LTP C1-INH.

The study authors concluded that the efficacy of C1-INH as a STP could only be shown for patients undergoing dental procedures; its efficacy for preventing attacks after other procedures could only be shown with controlled studies, which were lacking.[8] Evidence was also lacking regarding C1-INH use as a LTP but based on the limited evidence, the study authors concluded that C1-INH was effective at reducing the severity and number of HAE attacks.[8]

Randomized Study

In the RCT,[9] 24 patients participated initially, with two dropping out during the first period (one from each group), leaving 22 who completed the study (placebo = 11 patients, C1 inhibitor = 11 patients). The normalized average number of attacks during the two 12 week periods was 6.26 for C1 inhibitor, and 12.73 for placebo treatment. The mean severity of attacks was significantly lower on C1 inhibitor compared to placebo (1.3 ± 0.85 vs. 1.9 ± 0.36, $P < 0.001$; on a three point scale with 1 indicating a mild attack, and 3 indicating a severe attack). The duration of attacks was also statistically significantly shorter on C1 inhibitor compared to placebo (2.1 ± 1.13 vs. 3.4 ± 1.39 days, respectively, $P = 0.002$). Those receiving C1 inhibitor also experienced fewer days of swelling (10.1 ± 10.73 vs. 29.6 ± 16.9, respectively, $P < 0.001$). Patients were also eligible for C1 inhibitor open-label rescue therapy for acute attacks. Eleven patients on C1 inhibitor prophylaxis required an average of 4.7 injections compared to an average of 15.4 injections for 22 patients on placebo ($P < 0.001$). In terms of safety, 21 of 24 subjects experienced one or more AEs. Common AEs included sinusitis (5 patients), upper respiratory tract infection (4 patients), viral upper respiratory tract infection (3 subjects), vomiting (2 subjects), and gastro-

esophageal reflux disease (2 patients).[19] Three AEs were thought to be related to the study drug (lightheadedness, fever, and pruritus and rash).[9]

Non-Randomized Studies

For the registry study by Busse et al.,[10] a total of 135 patients reported at least one infusion of C1-INH. Of these 135 patients, C1-INH for solely prophylactic use was reported in 12 patients for 1582 infusions. Mean overall dose for prophylactic C1-INH use was 17.2 ± 4.8 IU/kg. The AE rate for prophylaxis was 0.14 per infusion (compared to an overall rate of 0.09 per infusion, and rate of 0.05 per infusion for acute treatment). While on C1-INH prophylaxis, two patients reported a disproportionately high number of AEs, administered every 3-4 days. When data from the patient with the highest number of AEs (a suspected outlier) was excluded, there was no trend noted between AE rate and C1-INH dose (coefficient of determination = 0.0005). Commonly reported AEs included gastrointestinal AEs (8.1% of patients), infection related AEs (7.4% of patients), and two patients had reported thromboembolic events (transient ischemic attack and deep vein thrombosis).

The survey by Nanda et al.[11] included 219 patients. Of these, 37 patients received STP before undergoing surgery (66 procedures); C1-INH was used as STP for 40 out of 66 procedures. Of these 37 patients, 8 (22%) reported a failure of STP, three of whom were receiving pdC1-INH.

In the study by Gavigan et al.,[12] 12 patients underwent 24 surgical procedures with STP use of C1-INH (10 to 20 U/kg administered IV 20-30 minutes before the procedure). No patients reported HAE attacks following the procedure (no time of follow-up specified). In eight of the procedures, patients also had LTP use of danazol.

Out of 20 patients receiving prophylactic C1-INH-nf in the study by Bernstein et al.,[13] 18 patients experienced an adverse event, the most common being URTI (25%) and nasopharyngitis (15%). Two patients experienced AEs related to the study drug (as determined by the investigator): one patient developed a medical device complication (“blood clot in port”), and one patient developed muscle spasms while undergoing the second stage of dosing. Two SAEs were reported: cerebral cystic hygroma in one patient, and one patient with a laryngeal angioedema attack (1st dosage stage) and then anemia and choledocholithiasis (2nd dosage stage) that required hospitalization. Per-protocol success was determined as ≤ 1 HAE attack per month; while investigator success was determined if a patient had a significant reduction from their historic attack rate, but experienced more than one HAE attack per month. Nine out of 20 patients experienced per-protocol success (four on 1500U and 5 on 2500U), two experienced investigator success (one on 1500U and one on 2500U), three patients experienced a reduction of more than 1 attack per month (one on 1500U and two on 2500U), six patients experienced failure (including two patients that discontinued).

Eleven patients received prophylactic C1-INH-nf during pregnancy in the study by Baker et al.[14] The number of doses ranged from 2 to 83. Three patients experienced HAE attacks while receiving prophylaxis, but experienced fewer attacks than their historical rates. Six patients did not experience HAE attacks, and data was not available for two subjects. Eight patients delivered nine neonates; one patient experienced spontaneous abortion (unrelated to study drug), one patient experienced a stillbirth (unrelated to study drug), one patient/infant outcome was lost to follow-up.

Lumry et al.[15] conducted a post-hoc retrospective analysis of the 2010 Zuraw RCT[9], addressing C1-INH use in children. Eight children in the acute treatment trial also received C1-INH-nf prophylaxis before 40 procedures (90% dental) with one reported HAE attack within 72 hours of preprocedural dosing. Additional analysis was done on results from a placebo-controlled trial and its open-label extension. Four children were included in the placebo-controlled trial, while 23 children were included in the prophylactic open-label extension.

The following summarizes the findings for the children included in the placebo-controlled study.[15] For patients on C1-INH-nf a two-fold reduction in number of HAE attacks was experienced when compared with placebo (mean number of attacks 7.0 vs. 13.0). The duration of attacks was 2.3 days on study drug, and 2.6 days on placebo. The duration of swelling was 9.0 days on study drug, and 20.8 days on placebo. A mean of 6.8 open-label, on demand treatment doses were used for patients on the study drug vs. 15.0 open-label, on demand treatments for those on placebo. One patient experienced an AE (unspecified) that was possibly related to study drug. No serious AEs were reported for the placebo-controlled trial.

For the open-label extension,[15] a median monthly number of attacks before the study drug intervention was 3.0, compared to 0.39 after. Out of 23 patients, 20 patients experienced ≤1 attack per month, five patients reported no attacks during the extension study period (up to 72 weeks). Seventeen out of 23 patients reported AEs, with two patients and three AEs related to the study drug (one patient with nausea and headache, and one patient with infusion-site erythema) and no serious AEs were reported during the extension study.

Farkas et al.,[16] reported that out of 54 patients, five experienced an attack after pdC1-INH STP. pdC1-INH was the most effective drug compared to danazol and tranexamic acid (TXA), when the proportion of patients experiencing edema after the intervention was considered (P = 0.0253, Fisher's exact test), when the number of patients experiencing an attack despite STP was considered (P = 0.0064, chi-square test), when the number of interventions followed by edema was considered (P = 0.0096, Fisher's exact test), and when the number of interventions resulting in edema formation were considered (P = 0.0202, chi-square test). The authors reported that no treatment-related AEs occurred with any of the study drugs.

In the study by Grant et al.,[17] C1-INH was administered within 24 hours before a surgical procedure as STP prophylaxis. It was reported that for 89 out of 91 procedures, an HAE attack did not occur within 72 hours following prophylactic dosing. The majority of the procedures were dental. In seven patients, 12 AEs were reported; three were SAEs (intestinal perforation, procedural pain, and B-cell lymphoma). Mild constipation was the only AE reported by more than one patient. None of the AEs were considered related to the study drug, or were considered associated with an HAE attack.

Zuraw and Kalfus[18] conducted an open-label extension for their previous clinical trial.[9] The analysis included 146 subjects. When compared to historical monthly rates (mean attack frequency = 4.7 ± 5.2; median attack frequency = 3 [Interquartile Range (IQR), 2-4]) there was a statistically significant reduction in monthly attack rates (mean attack frequency = 0.47 ± 0.83; median attack frequency 0.19 [IQR, 0.0-0.64], P < 0.001). Overall attack frequencies varied, 128 reporting ≤1 attack per month, including the 51 participants who reported no attacks during the study period, and 18 patients reporting >1 attack per month. There was a statistically significant correlation regarding the interval between injections (in days) and the frequency of attacks (R = 0.911, P < 0.001). Patients were on the study drug for a median duration of 248 days (range of 173-507 days). Two out of 101 SAEs (major depression and musculoskeletal chest pain) had an

unknown relationship to the study drug. The remaining 99 AEs were considered unrelated to the study drug. Five patients experienced SAEs related to thromboembolic events, though none were considered related to the study drug as patients had underlying risk factors for these events.

What is the cost-effectiveness of C1 esterase inhibitor as prophylaxis against hereditary angioedema attacks?

No summary can be provided for the cost-effectiveness of C1 esterase inhibitor as prophylaxis against HAE attacks as no relevant literature was identified.

What are the evidence-based guidelines for the prophylactic use of C1 esterase inhibitor in hereditary angioedema?

One evidence-based guideline was identified.[4] Recommendations stated that for some patients, pdC1-INH is effective for LTP; this recommendation was graded as having a high level of evidence, and the strength of the recommendation was strong. Additionally, to use C1-INH as LTP, it was not deemed necessary to fail other LTP therapies; the level of evidence for this recommendation was expert opinion, and the strength of the recommendation was strong.

Limitations

Major limitations to this report include the lack of cost-effectiveness data regarding the prophylactic use of C1-INH. High quality systematic reviews and randomized controlled trials were also lacking. More high quality evidence is needed regarding prophylactic use of C1-INH for the prevention of HAE attacks.

While evidence was found regarding the clinical effectiveness of prophylactic C1-INH for the prevention of HAE attacks, as already noted, these studies were marked by many limitations and the findings should be interpreted with a degree of caution. Due to the rare nature of the disease, large scale clinical trials were not possible, and the included RCT[9] had a small number of patients participate. The systematic review[8] included only a descriptive summary of the identified studies, as meta-analysis was not feasible or appropriate, and was limited in the scope of study drug (restricted to Berinert). Findings from the review may not be applicable to other C1-INH products.

Lack of control or comparator groups is also a limitation of the studies included in this report. The majority of the studies did not have any comparators or controls groups.[8,10-14,17,18] While some conclusions can be drawn regarding the clinical effectiveness of C1-INH in general, there is limited information on how C1-INH compares to placebo, or other HAE management and prevention treatment therapies. This limits the knowledge about the place of C1-INH in therapy. The studies that did include comparator data, either placebo[9,15] or other treatment therapies,[16] were marked by their own set of limitations, including uncertain blinding and patient allocation,[9,15] small number of patients,[9,15] and lack of randomization.[16]

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

One systematic review,[8] one RCT,[9] nine non-randomized studies,[10-18] and one evidence-based guideline[4] were identified regarding the prophylactic use of C1-INH for hereditary angioedema attacks. No cost-effectiveness studies were identified. All studies, including the evidence-based

guidelines, found C1-INH to be effective in the prevention of HAE attacks when used as either short-term prophylaxis or long-term prophylaxis. However, these studies are marked by several limitations, and the findings should be interpreted with caution.

Safety was also an outcome of interest for all studies, with one study[18] reporting adverse events (AEs) with an unknown relationship to C1-INH use, and one study[9] reporting AEs thought to be related to C1-INH use.[9] Major depression and musculoskeletal chest pain were reported AEs with an unknown relationship to the C1-INH use; lightheadedness, fever, and pruritus and rash were AEs thought to be related to C1-INH use.[9] A retrospective, post-hoc analysis of the RCT data for pediatric patients, reported two children with three AEs related to C1-INH use; these included nausea and headache, and infusion-site erythema.[15] Zuraw and Kalfus[18] reported serious AEs related to thromboembolic events, though there was no reported association with C1-INH use. Additionally, Busse et al.[10] reported two patients with thromboembolic events.

With regards to patient populations studied, most studies included adult and pediatric patients,[10,13,14,16-18] did not specify age,[8,11] reported only on pediatric patients,[15] or reported only on C1-INH use in adults.[12] Two non-randomized studies specifically reported on prophylaxis in vulnerable patient populations; one regarding the use of C1-INH in pregnant patients[14], and one regarding use in pediatric patients.[15] The identified guidelines[4] did not specifically address pediatric or obstetric patients, but rather were generally applicable to HAE patients.

According to the identified studies and guideline, the use of C1-INH for the prophylaxis of HAE attacks is clinically effective and relatively safe. This includes its use as a short-term prophylactic before surgical or invasive procedures, or as a long-term prophylaxis agent. This was found for patients of all ages, including vulnerable patient populations such as pregnant women. However, due to the lack of high quality data, and lack of comparator or control data, there are many limitations and the findings should be interpreted with caution. The prophylactic use of C1-INH in clinical practice may depend on a patient's disease history, including responses to other therapies, attack severity, attack frequency, and exposure to known HAE attack triggers (i.e., surgical procedures). Lack of cost-effectiveness data additionally limits the application of these findings, as C1-INH has an unclear place in therapy for the general HAE population. More high quality trials, and cost-effectiveness data, are needed in regards to the prophylactic use of C1-INH in the prevention of HAE attacks.

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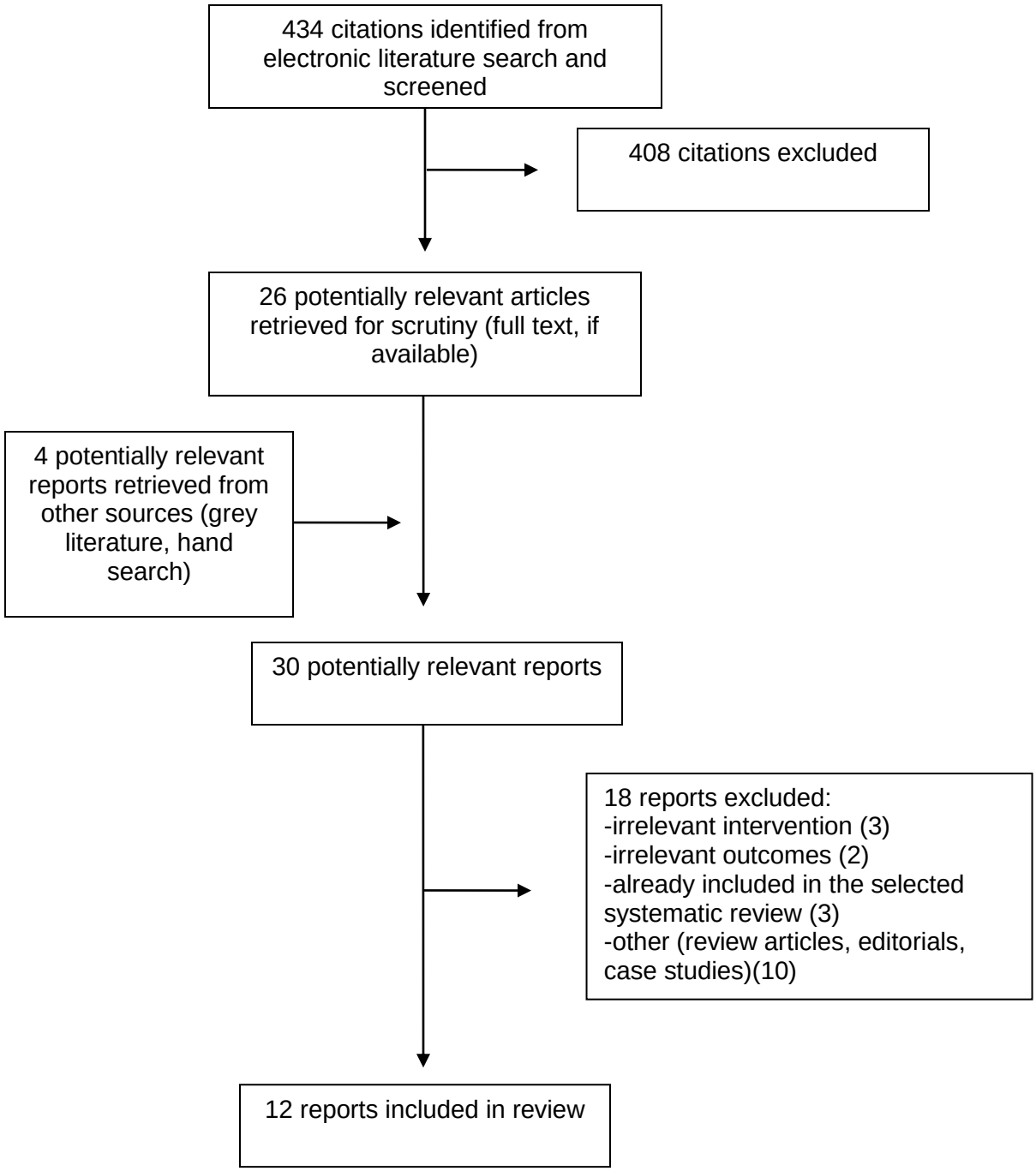
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Bork (2013)[8] Germany	STP: 195 patients, 293 instances (6 case-series studies, 4 retrospective survey studies, 1 retrospective/ prospective cohort study, 1 retrospective cohort study, 1 prospective/retrospective survey study, 21 case reports) LTP: 90 patients (1 prospective cohort study, 1 retrospective survey study, 1 prospective cohort study, 5 case reports)	Patients with type I or type II HAE	STP and LTP with C1-INH	N/A	Clinical effectiveness, safety

C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema; LTP = long-term prophylaxis; N/A = not applicable; STP = short-term prophylaxis

Table A2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Randomized Controlled Trial					
Zuraw (2010)[9] USA	RCT	22 HAE patients	C1-INH 1000 U every 3-4 days	Placebo	Clinical effectiveness, safety
Non-Randomized Studies					
Busse (2015)[10] USA	Non-comparative, observational, open patient registry	Prophylaxis: 12 patients; 1582 infusions Total: 135 patients; 3196 infusions	Prophylactic C1-INH use	N/A	Safety
Nanda (2014)[11] USA	Patient and physician survey	219 patients with type 1 and type 2 HAE Prophylaxis: 12/135 patients	Prophylactic C1-INH use	N/A	Clinical effectiveness, safety

Table A2: Characteristics of Included Clinical Studies					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
		Both acute and prophylaxis: 31/135 patients			
Gavigan (2014)[12] Canada	Retrospective chart review	12 patients (24 surgical procedures) with type 1 HAE	Prophylactic C1-INH use	N/A	Safety
Bernstein (2013)[13] USA	Phase 4, open-label trial	20 patients with HAE	Escalating doses of prophylactic C1-INH (1500 U, 2000 U, 2500 U)	N/A	Clinical effectiveness, safety
Baker (2013)[14] USA	Retrospective analysis of open-label trial data	11 pregnant patients with HAE	Prophylactic C1-INH use	N/A	Clinical effectiveness, safety
Lumry (2013)[15] USA	Post hoc analysis of randomized, placebo-controlled studies and open-label extensions	4 pediatric patients in the placebo-controlled prophylaxis study; 11 pediatric patients in the open-label prophylaxis study	Placebo-controlled prophylaxis study: IV C1-INH 1000 U every 3-4 days; Open-label prophylaxis study: IV C1-INH 1000 U every 3-7 days	Placebo; N/A	Clinical effectiveness, safety
Farkas (2012)[16] Hungary	Prospective cohort study	137 patients; 87 cases of STP with pdC1-INH	pdC1-INH 500 IU via IV 1 hour before procedure	Danazol, TXA	Clinical effectiveness, safety
Grant (2012)[17] USA	Post hoc analysis of randomized, placebo-controlled studies and open-label extensions	91 procedures with STP C1-INH-nf in 41 subjects	C1-INH-nf 100 U administered IV within 24 hours before procedure	N/A	Clinical effectiveness, safety
Zuraw (2012)[18] USA	Open-label extension study	146 patients	C1-INH-nf 1000 U every 3-7 days	N/A	Clinical effectiveness, safety

C1-INH = C1 esterase inhibitor; C1-INH-nf = C1-INH nano-filtered; HAE = hereditary angioedema; N/A = not applicable; RCT = randomized controlled trial; STP = short term prophylaxis; TXA = tranexamic acid; U = units; USA = United States of America

Table A3: Characteristics of Included Guidelines						
Objectives			**Methodology**			
Intended users/ Target population	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendations development and Evaluation**	**Guideline Validation**
Betschel, 2014[4] – Canadian Hereditary Angioedema Guideline Committee						
Health care providers involved in the care of patients with HAE	HAE management	C1-INH use in STP and LTP	Systematic review, and recommendations assessed by adapted GRADE	Varied by recommendation	Guideline development group and systematic review of the evidence	Not stated

C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema; LTP = long-term prophylaxis; STP = short-term prophylaxis

APPENDIX 3: Critical Appraisal of Included Publications

Table A4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[6]

Strengths	Limitations
Bork[8]	
• Clearly stated objectives and key research questions • Duplicate study selection and data extraction	• No meta-analysis was performed • No appraisal of included studies was provided • Uncertain generalizability to C1-INH products other than Berinert (CSL Behring, Marburg, Germany) • Unclear search strategy (no MESH terms provided) • There was no exploration into publication bias

C1-INH = C1 esterase inhibitor

Table A5: Strengths and Limitations of Randomized Controlled Trials using Downs and Black[5]

Strengths	Limitations
Zuraw[9]	
• Randomized, placebo-controlled trial, which allowed for comparison of C1-INH to a control group • Clearly stated objective, and primary outcomes	• Patients participating in the trial may not be representative of the source population, as inclusion criteria was a high frequency of HAE attacks • Findings may not be generalizable to the greater HAE population, as characteristics of patients participating in RCTs may differ from the other HAE patients • Possible confounding effect of baseline androgen therapy in 3/22 patients, with no further exploration in the main results • Uncertain blinding of patients and investigators

C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema; RCT = randomized-controlled trial

Table A6: Strengths and Limitations of Clinical Studies using Downs and Black[6]

Strengths	Limitations
Busse[10]	
• Clearly stated objective and main findings • Multicentre, multinational patient registry • Use of C1-INH by patients in the registry is likely reflective of clinical practice	• Non-comparative, non-randomized study • External validity may be limited as the patient population was not ethnically diverse • Included data collected retrospectively, and subject to biases (e.g., recall or reporting bias) • Patients participating in the registry may not be representative of the greater HAE population, and as such, the registry may be subject to selection bias

Table A6: Strengths and Limitations of Clinical Studies using Downs and Black[6]	
Strengths	**Limitations**
Nanda[11]	
• Clearly stated objectives and patient characteristics • Large survey of HAE patients	• Non-comparative, non-randomized study • HAE was self-reported and only the first 250 survey responses were included, this may subject the study to selection bias • Recall bias may interfere with responders answers • Definition of short term prophylactic failure is vague and questions regarding failure may be misinterpreted by responders
Gavigan[12]	
• Clearly stated objectives and primary outcomes • Clearly stated study intervention, including dosing of C1-INH	• Non-comparative, non-randomized study • Small number of patients • Retrospective design may include biases • Long duration of study, and variable doses, may not be representative of current practice and have limited generalizability • Possible confounding from a few patients with concomitant attenuated androgen use was not explored
Bernstein[13]	
• Clearly stated objective, primary outcomes, main findings, and adverse events • Patients were followed for the same length of time, and reasons for discontinuation of study participants was clearly reported	• Not powered to determine drug efficacy • Open-label, non-randomized study • Uncertain external validity as circumstances for drug administration (e.g. setting and dose) may not reflect clinical practice
Baker[14]	
• Clearly stated objectives and primary outcomes • Provided adequate justification for lack of control or comparator (e.g., unethical considering vulnerable patient population)	• Open-label, non-randomized study • Small number of patients • Lack of control group prevented any statistical analysis, descriptive statistics reported • Uncertain external validity for other pregnant patients, as these patients were part of studies with other primary objectives (not related to pregnancy)
Lumry[15]	
• Clearly stated objective, primary outcomes, and main findings • Provided adequate justification for lack of control or comparator (e.g., unethical considering vulnerable patient population)	• Post hoc analysis of previous clinical trial data, including open-label, non-randomized data • No comparison to placebo or other drugs • Uncertain external validity for other pediatric patients, as these patients were part of studies with other objectives (not related to pediatrics)

Table A6: Strengths and Limitations of Clinical Studies using Downs and Black[6]	
Strengths	**Limitations**
Farkas[16]	
• Clearly stated objective, and interventions • Comparison of intervention to other drugs	• Non-randomized • Uncertain patient recruitment, which may result in selection bias and limited generalizability to other HAE patients
Grant[17]	
• Clearly stated objectives and study outcomes	• Post hoc analysis of previous clinical trial data, including open-label, non-randomized data • No comparison to placebo or other drugs • Possible recall bias, as case report forms were filled out post hoc by physicians
Zuraw[18]	
• Large number of patients • Clearly stated objective, and primary outcomes	• Open-label, non-randomized study • No comparison to placebo or other drugs • Uncertain patient recruitment, which may result in selection bias and limited generalizability to other HAE patients

C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema

Table A7: Strengths and Limitations of Guidelines using AGREE II[7]	
Strengths	**Limitations**
Betschel[4]	
• Included studies were appraised for quality • Recommendations were graded according to a defined grading system • Recommendations include clinical considerations to provide context	• Uncertain methodology for review (i.e., whether multiple reviewers performed screening, data extraction, etc.) • Costs and barriers of guidance implementation not evaluated • Special populations (i.e., pediatric and obstetric patients) not specifically addressed • Uncertain guideline validation

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A8: Summary of Findings of Systematic Reviews

Main Study Findings	Author's Conclusions
Bork (2013)[8]	
Short-term prophylaxis (STP) • 195 patients for 293 occasions • The majority (155) were for dental procedures • 1 cohort study reported no HAE complications for two patients administered C1-INH 30 minutes before surgery • 1 cohort study (171 patients for 705 tooth extractions) had a rate of facial swelling or laryngeal edema of 21.5% of 577 extractions when prophylaxis was not used, vs. 12.5% of 138 extractions where prophylaxis was used • 5 survey studies (64 cases) reported no cases of HAE when C1-INH was used as prophylaxis • 1 case study reported on the use of C1-INH 1 hour before surgery for 71 procedures in 51 patients, with no cases of angioedema • 0 cases of HAE occurred in an additional five case series (10 cases), and 21 case reports *Long-term prophylaxis (LTP)* • 1 prospective cohort study - reduction in symptom intensity (14 patients received C1-INH as LTP for an average of nine years (93.3% of attacks were considered severe without the use of prophylaxis, compared to 3.8% with prophylaxis)) • Decrease in attack frequency was reported by another prospective cohort study (15 out of 30 patients who before treatment had previously experienced one or two attacks per week did not report any HAE attacks while on LTP (C1-INH two to three times per week)) • 1 retrospective study reported no episodes of HAE for two pregnant patients (500 U pdC1-INH IV, once per week) • 5 cases studies reported adequately controlled HAE with the use of LTP	"Short-term prophylaxis with C1-INH was shown to prevent HAE attacks after dental procedures. Likewise, HAE attacks were absent after prophylactic use in various other medical interventions. Long-term prophylaxis with C1-INH significantly decreased the frequency of severe attacks in patients experiencing frequent and/or debilitating attacks." (pg. 324).

C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema; IV = intravenous; LTP = long-term prophylaxis; pdC1-INH = plasma-derived C1-INH; STP = short term prophylaxis; U = units

Table A9: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
Randomized controlled trial	
Zuraw (2010)[9]	
• 24 patients with 2 dropping out (one from each group) • 22 for analysis (placebo = 11 patients, C1 inhibitor = 11 patients) • Normalized average number of attacks during the two 12 week periods was 6.26 for C1 inhibitor, and 12.73 for placebo treatment • Mean severity of attacks was significantly lower on C1 inhibitor compared to placebo (1.3 ± 0.85 vs. 1.9 ± 0.36, *P* < 0.001) • Duration of attacks was also statistically significantly shorter on C1 inhibitor compared to placebo (2.1 ± 1.13 vs. 3.4 ± 1.39 days, respectively, *P* = 0.002) • Those receiving C1 inhibitor experienced fewer days of swelling (10.1 ± 10.73 vs. 29.6 ± 16.9, respectively, *P* < 0.001) • 11 patients on C1 inhibitor prophylaxis required open-label rescue therapy, compared to 22 patients on placebo • C1 inhibitor was also associated with fewer open-label injections compared to placebo (4.7 ± 8.66 vs. 15.4 ± 8.41, *P* < 0.001) • 21/24 subjects experienced one or more AEs • 3 AEs were thought to be related to the study drug (lightheadedness, fever, and pruritus and rash)	"In both studies, the need for additional, rescue injections suggests that in some cases a higher dose or more frequency injections of C1 inhibitor might have been beneficial. Thus, the optimal dose of nanofiltered C1 inhibitor concentrate for either treatment or prophylaxis remains uncertain." (pg. 521). "When used for prophylaxis, C1 inhibitor significantly reduced the frequency of acute attacks, as compared with placebo." (pg. 521).
Observational Studies	
Busse (2015)[10]	
• 135 patients • C1-INH for solely prophylactic use was reported in 12 patients for 1582 infusions • Both prophylaxis and acute treatment in 31 patients • Mean overall dose of C1-INH was 17.2 ± 4.8 IU/kg; prospective dosing was 18.2 ± 4.5 IU/kg, and retrospective dosing was 13.2 ± 3.6 IU/kg • AE rate for prophylaxis was 0.14 per infusion, compared to an overall rate of 0.09 per infusion, and rate of 0.05 per infusion for acute treatment	"The registry findings confirm a high level of safety with C1-INH use for the indication of HAE for either acute treatment or prophylaxis, regardless of the dose or administration setting." (pg. 217).

Table A9: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
• 2 patients reported a disproportionately high number of AEs while on C1-INH prophylaxis, administered every 3-4 days • Patient with the highest number of AEs (suspected outlier) was excluded, no trend noted between AE rate and C1-INH dose (coefficient of determination = 0.0005) • 2 patients had reported thromboembolic events.	
Nanda (2014)[11]	
• Survey included 219 patients • Only 37 patients received STP before undergoing surgery (66 procedures) • Of these 37 patients, 8 (22%) reported a failure of STP, 3 of whom received pdC1-INH	"The most commonly used STP medication reported by physicians was pdC1INH…" (pg. 201). "Physicians reported excellent efficacy of preprocedure STP, whereas patients receiving STP reported a 22% (n = 8 of 37) breakthrough attack rate." (pg. 202).
Gavigan (2014)[12]	
• 12 patients underwent 24 surgical procedures with STP • 10 to 20 U/kg of C1-INH administered IV 20-30 minutes before the procedure • No patients reported HAE attacks following the procedure (no time of follow-up specified). In eight of the procedures, patients also had LTP use of danazol	"In our experience, C1 INH was an effective short-term prophylactic treatment for Type I HAE patients undergoing invasive procedures. There were no post-procedural HAE attacks following any of the 24 procedures." (pg. 2).
Bernstein (2013)[13]	
• 18/20 patients experienced an AE • Most common AEs: URTI (25%) and nasopharyngitis (15%) • 2 patients experienced AEs related to the study drug ("blood clot in port", and muscle spasms) • 2 SAEs: cerebral cystic hygroma; laryngeal angioedema attack and then anemia and choledocholithiasis • 9/20 patients experienced per-protocol success (4 on 1500U and 5 on 2500U) • 2 experienced investigator success (1 on 1500U and one on 2500U) • 3 patients experienced a reduction of more than 1 attack per month (1 on 1500U and 2 on 2500U) • 6 patients experienced failure (including 2 patients that discontinued)	"The results of our study indicated that the safety profile of C1 INH-nf doses up to 2500 U every 3 or 4 days for 6 months is consistent with the known safety profile at the approved 1000-U regimen. Most adverse events were mild or moderate in intensity and were not serious. No patients discontinued C1 INH-nf treatment because of an adverse event." (pg. 83).

Table A9: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
Baker (2013)[14]	
• 11 patients received prophylactic C1-INH-nf during pregnancy • Number of doses ranged from 2-83 • 3 patients experienced HAE attacks while receiving prophylactic • 6 patients did not experience HAE attacks • Data is unknown for 2 subjects • 8 patients delivered 9 neonates • 1 patient experienced spontaneous abortion (unrelated to study drug) • 1 patient experienced a stillbirth (unrelated to study drug • 1 patient/infant outcome lost to follow-up.	"… C1 INH-nf appeared to be safe in the treatment and prevention of attacks during pregnancy and delivery. Duration of exposure of the fetus to C1 INH-nf ranged from 1 day to a full pregnancy term, which reflects diverse clinical scenarios." (pg. 167).
Lumry (2013)[15]	
STP use in the acute treatment study • 8 children received C1-INH-nf prophylaxis before 40 procedures (90% dental) • 1 reported HAE attack within 72 hours *Placebo-controlled* • 2-fold reduction in number of HAE attacks was experienced when compared with placebo (mean 7.0 vs. 13.0) • Duration of attacks was 2.3 days on study drug, vs 2.6 days on placebo • Duration of swelling was 9.0 days on study drug vs. 20.8 days on placebo • Mean of 6.8 open-label, on demand treatment doses were used for patients on the study drug vs. 15.0 open-label, on demand treatment for those on placebo • 1 patient experienced an AE (unspecified) that was possibly related to study drug • No serious AEs were reported *Open-label* • Median monthly attack before the study drug intervention was 3.0, vs. to 0.39 after • 20/23 experienced ≤1 attack per month • 5 patients reported no attacks during the study period (up to 72 weeks) • 17/23 patients reported AEs • 2 patients with 3 AEs related to study drug (one patient with nausea and headache, and one patient with infusion-site erythema) • No serious AEs were reported	"… those who received prophylaxis therapy had a reduced monthly attack rate. Taken together, these data offer a substantive body of evidence supporting the clinical utility of C1 INH-nf in children with HAE." (pg. 1021).

Table A9: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
Farkas (2012) [16]	
• 5/54 experienced an attack after pdC1-INH STP • pdC1-INH was the most effective drug compared to Danazol and TXA when the proportion of patients experiencing edema after the intervention was considered (*P* = 0.0253, Fisher's exact test) • When the number of patients experiencing an attack despite STP was considered (*P* = 0.0064, chi-square test) • When the number of interventions followed by edema was considered (*P* = 0.0096, Fisher's exact test) • When the number of interventions resulting in edema formation were considered (*P* = 0.0202, chi-square test) • No treatment-related AEs occurred with any of the study drugs	"Comparing the efficacy of three medicinal products used in this study, edematous episodes occurred significantly less frequently after STP with C1-INH concentrate (Berinert®, CSL Behring, Marburg, Germany) than following the prophylactic administration of danazol, or TXA (6%, *vs* 13%, *vs* 33% of cases, respectively)." (pg. 1590-1591).
Grant (2012)[17]	
• 89/91 procedures - HAE did not occur within 72 hours • In 7 patients, 12 AEs were reported; three were SAEs (intestinal perforation, procedural pain, and B-cell lymphoma) • Mild constipation was the only AE reported by one than one patient (2 patients) • None of the AEs were considered related to the study drug	"The results of this analysis provide further support for the efficacy and safety of preprocedural administration of C1 INH-nf (human) for the prevention of HAE attacks." (pg. 352).
Zuraw (2012)[18]	
• Analysis included 146 subjects • Compared to historical monthly rates (mean attack frequency = 4.7 ± 5.2; median attack frequency = 3 (IQR, 2-4)) there was a statistically significant reduction in monthly attack rates (mean attack frequency = 0.47 ± 0.83; median attack frequency 0.19 (IQR, 0.0-0.64)) (*P* < 0.001) • 51 reporting no attacks during the study • 128 reporting ≤1 attack per month • 18 patients reporting >1 attack per month • Correlation regarding the interval between injections (in days) and the frequency of attacks (*R* = 0.911, *P* < 0.001) • Patients were on the study drug for a median duration of 248 days (range of 173-	"The open-label study demonstrates that prophylactic C1INH-nf therapy at the recommended dose of 1000 units twice per week was highly effective, durable, and safe in the majority of patients with hereditary angioedema." (pg. 938.e6). "Hereditary angioedema was not well controlled even at twice-weekly dosing in a relatively small fraction of the subjects; whether these subjects would benefit from a higher dose per injection was not addressed in this study." (pg. 938.e6).

Table A9: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
507 days) • 5 patients experienced SAEs related to thromboembolic events, • 2/101 AEs were considered serious in nature (major depression and musculoskeletal chest pain) and had an unknown relationship to the study drug • Remaining 99 AEs considered unrelated to the study drug	

AEs = adverse events; C1-INH = C1 esterase inhibitor; C1-INH-nf = C1-INH nano-filtered; HAE = hereditary angioedema; IQR = interquartile range; LTP = long-term prophylaxis; pdC1-INH = plasma-derived C1-INH; SAE = serious adverse event; STP = short term prophylaxis; TXA = tranexamic acid; U = units

Table A10: Summary of Findings of Included Guidelines
Recommendations
Canadian Hereditary Angioedema Guideline Committee (2014)[4]
Recommendation 16: "Plasma-derived C1-INH is effective for long-term prophylaxis in some patients." (pg. 10) Level of evidence and strength of recommendation is high and strong, respectively. Recommendation 18: "It is not necessary to fail other long-term prophylaxis therapies before use of C1-INH for long-term prophylaxis is considered." (pg. 11) Level of evidence and strength of recommendation is expert opinion and strong, respectively.

C1-INH = C1 esterase inhibitor